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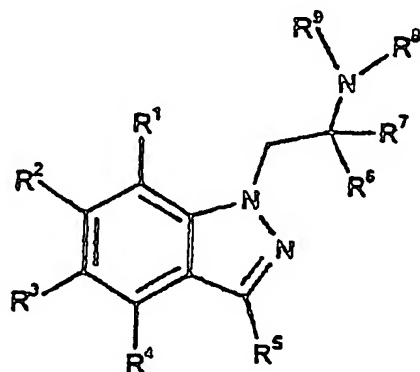
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(54) Title: 6-HYDROXY-INDAZOLE DERIVATIVES FOR TREATING GLAUCOMA



(1)

(57) Abstract: Substituted 1-( $\alpha$ -alkyl-ethylamino)-1H-indazol-6-ols  
useful for lowering and controlling IOP and treating glaucoma are dis-  
closed.

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## 6-HYDROXY-INDAZOLE DERIVATIVES FOR TREATING GLAUCOMA

The present invention is directed to novel substituted 1-( $\alpha$ -alkyl-ethylamino)-1*H*-indazol-6-ols. These novel compounds are useful for lowering and controlling normal or elevated intraocular pressure (IOP) and treating glaucoma.

### Background of the Invention

The disease state referred to as glaucoma is characterized by a permanent loss of visual function due to irreversible damage to the optic nerve. The several morphologically or functionally distinct types of glaucoma are typically characterized by elevated IOP, which is considered to be causally related to the pathological course of the disease. Ocular hypertension is a condition wherein intraocular pressure is elevated but no apparent loss of visual function has occurred; such patients are considered to be a high risk for the eventual development of the visual loss associated with glaucoma. Some patients with glaucomatous field loss have relatively low intraocular pressure. These so called normotension or low tension glaucoma patients can also benefit from agents that lower and control IOP. If glaucoma or ocular hypertension is detected early and treated promptly with medications that effectively reduce elevated intraocular pressure, loss of visual function or its progressive deterioration can generally be ameliorated. Drug therapies that have proven to be effective for the reduction of intraocular pressure include both agents that decrease aqueous humor production and agents that increase the outflow facility. Such therapies are in general administered by one of two possible routes, topically (direct application to the eye) or orally.

There are some individuals who do not respond well when treated with certain existing glaucoma therapies. There is, therefore, a need for other topical therapeutic agents that control IOP.

It has been found that serotonergic compounds which possess agonist activity at 5-HT<sub>2</sub> receptors effectively lower and control normal and elevated IOP and are useful for treating glaucoma, see commonly owned co-pending application, PCT/US99/19888. Compounds that act as agonists at 5-HT<sub>2</sub> receptors are well known and have shown a variety of utilities, primarily for disorders or conditions associated with the central nervous system (CNS). U.S. Patent 5,494,928 discloses certain 2-(indol-1-yl)-ethylamine derivatives that are 5-HT<sub>2C</sub> agonists for the treatment of obsessive compulsive disorder and other CNS derived personality disorders. U.S.

Patent 5,571,833 discloses tryptamine derivatives that are 5-HT<sub>2</sub> agonists for the treatment of portal hypertension and migraine. U.S. Patent 5,874,477 discloses a method for treating malaria using 5-HT<sub>2A/2C</sub> agonists. U.S. Patent 5,902,815 discloses the use of 5-HT<sub>2A</sub> agonists to prevent adverse effects of NMDA receptor hypo-  
5 function. Published International Patent Application No. WO98/30548 discloses that selected 1-ethylamino-1*H*-indazoles substituted at ring positions 4-, 5-, 6-, or 7- have selective affinity for the 5-HT<sub>2C</sub> receptor and thereby have utility in the treatment of central nervous system diseases. International Patent Application Nos. WO00/12481 and WO00/17170 disclose yet other 1-ethylamino-1*H*-indazoles that have selective  
10 affinity for the 5-HT<sub>2C</sub> receptor and thereby have utility in the treatment of disorders of the central nervous system. Published International Patent Application No. WO98/31354A2 discloses 5-HT<sub>2B</sub> agonists for the treatment of depression and other CNS conditions. WO00/35922 discloses certain pyrazino[1,2-*a*]quinoxaline derivatives as 5-HT<sub>2C</sub> agonists for the treatment of obsessive-compulsive disorder,  
15 depression, eating disorders, and other disorders involving the CNS. Agonist response at the 5-HT<sub>2A</sub> receptor is reported to be the primary activity responsible for hallucinogenic activity, with some lesser involvement of the 5-HT<sub>2C</sub> receptor possible [Psychopharmacology, Vol. 121:357, 1995].

20 The present invention is directed to novel substituted 1-( $\alpha$ -alkyl-ethylamino)-1*H*-indazol-6-ols. It has been determined that these novel compounds have a high affinity for and function as agonists at the serotonergic 5-HT<sub>2</sub> receptor, and are useful for lowering and controlling normal or elevated intraocular pressure (IOP) and treating glaucoma. When a phenolic moiety is included in this substitution, e.g. a hydroxyl  
25 group at indazole ring position six, such compounds can be particularly sensitive to oxidation reactions well known to occur with phenolic compounds in general, including hydroxytryptamines [*J. Phys. Chem.* 103, 8606 (1999), *Chem. Res. Toxicol.* 11, 639 (1998), *J. Org. Chem.* 52, 2817 (1987), *J. Pharm. Sci.* 77, 911 (1988)], which are of particular relevance to the present application. Protection of such phenols from  
30 oxidation can be accomplished by derivatization of the aryl hydroxyl group to provide a suitable ester, carbamate, or carbonate. Though the ester, carbamate, or carbonate derivatives do not themselves possess a high affinity for the above mentioned receptors, they do have utility in the treatment of glaucoma since suitably protected phenols can be cleaved in vivo either by chemical hydrolysis or through the action of  
35 tissue esterases, thereby delivering the desired therapeutic agent, that is, the desired novel 6-hydroxy-indazole compounds of the present invention. The concept of utilizing such derivatized phenolic compounds as chemical delivery agents is well known in the art [*Drugs Pharm. Sci.* 53, 221 (1992), *Pharm. Res.*, 168 (1984)].

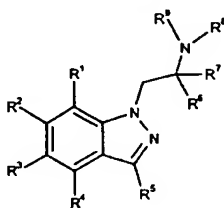
### Summary of the Invention

The present invention is directed to new and known derivatives of 1-(ethylamino)-1*H*-indazole that can be used to lower and control IOP associated with normal-tension glaucoma, ocular hypertension, and glaucoma in warm-blooded animals, including man. The compounds are formulated in pharmaceutical compositions suitable for topical delivery to the eye.

### Description of the Preferred Embodiments

Compounds that are useful according to the present invention are represented by the following Formula I.

#### FORMULA I



wherein  $R^1$  to  $R^4$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl, trifluoromethyl, O-W,  $C_{1-6}$ alkylthio,  $C_{1-6}$ alkylsulfoxyl,  $C_{1-6}$ alkylsulfonyl, or cyano;  $R^5$  can be hydrogen,  $C_{1-6}$ alkyl, or  $C_{1-4}$ alkoxy, halogen, trifluoromethyl, cyano,  $NR^{10}R^{11}$ ;

$R^6$  and  $R^7$  are independently chosen from hydrogen,  $C_{1-4}$ alkyl or  $R^6$ ,  $R^7$  and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore,  $R^7$  and  $R^8$  together can be  $(CH_2)_m$  to form a saturated heterocycle;

$R^8$  and  $R^9$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl;

$R^{10}$  and  $R^{11}$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl, or  $R^{10}$ ,  $R^{11}$  and the nitrogen atom to which they are attached can form a saturated heterocyclic ring selected from pyrrolidine, piperidine, piperazine, or morpholine;

$R^1$  to  $R^4$  cannot simultaneously be hydrogen;

$R^6$  and  $R^7$  cannot both be hydrogen;

W is hydrogen,  $C_{1-4}$ alkyl,  $C(=O)X$ , or  $P(=O)(OY)(OZ)$ ;

X is  $C_{1-6}$ alkyl,  $NR^8R^9$ ,  $N(R^8)CH_2(CH_2)_nC(=O)N(R^8)(R^9)$ ,  $OC_{1-6}$ alkyl,  $C_{1-6}$ alkyl (which can be substituted with halogen, hydroxyl,  $CO_2C_{1-4}$ alkyl,  $CON(C_{1-4}alkyl)_2$ ,

C(=NH)NH<sub>2</sub>, NHC(=NH)NH<sub>2</sub>, NH<sub>2</sub>), C<sub>2-4</sub>alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy or halogen); Y and Z are independently chosen from hydrogen, C<sub>1-10</sub> alkyl or Y and Z can together form a lower alkyl chain of (CH<sub>2</sub>)<sub>m</sub>;

m is 2 – 4;

n is 1 or 2;

and pharmaceutically acceptable salts and solvates of the compounds of Formula I.

Compounds that are novel and which are useful according to the present invention can be defined as follows:

wherein R<sup>1</sup> to R<sup>4</sup> are independently chosen from hydrogen, halogen, C<sub>1-6</sub>alkyl, trifluoromethyl, O-W, C<sub>1-6</sub>alkylthio, C<sub>1-6</sub>alkylsulfoxyl, C<sub>1-6</sub>alkylsulfonyl, or cyano;

R<sup>5</sup> can be halogen, trifluoromethyl, cyano, NR<sup>10</sup>R<sup>11</sup>;

R<sup>6</sup> and R<sup>7</sup> are independently chosen from hydrogen, C<sub>1-4</sub>alkyl or R<sup>6</sup>, R<sup>7</sup> and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore, R<sup>7</sup> and R<sup>8</sup> together can be (CH<sub>2</sub>)<sub>m</sub> to form a saturated heterocycle;

R<sup>8</sup> and R<sup>9</sup> are independently chosen from hydrogen or C<sub>1-4</sub>alkyl;

R<sup>10</sup> and R<sup>11</sup> are independently chosen from hydrogen or C<sub>1-4</sub>alkyl, or R<sup>10</sup>, R<sup>11</sup> and the nitrogen atom to which they are attached can form a saturated heterocyclic ring selected from pyrrolidine, piperidine, piperazine, or morpholine;

R<sup>1</sup> to R<sup>4</sup> cannot simultaneously be hydrogen;

R<sup>6</sup> and R<sup>7</sup> cannot both be hydrogen;

W is hydrogen, C<sub>1-4</sub>alkyl, C(=O)X, or P(=O)(OY)(OZ);

X is C<sub>1-6</sub>alkyl, NR<sup>8</sup>R<sup>9</sup>, N(R<sup>8</sup>)CH<sub>2</sub>(CH<sub>2</sub>)<sub>n</sub>C(=O)N(R<sup>8</sup>)(R<sup>9</sup>), OC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl (which can be substituted with halogen, hydroxyl, CO<sub>2</sub>C<sub>1-4</sub>alkyl, CON(C<sub>1-4</sub>alkyl)<sub>2</sub>,

C(=NH)NH<sub>2</sub>, NHC(=NH)NH<sub>2</sub>, NH<sub>2</sub>), C<sub>2-4</sub>alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy or halogen);

Y and Z are independently chosen from hydrogen, C<sub>1-10</sub> alkyl or Y and Z can together form a lower alkyl chain of (CH<sub>2</sub>)<sub>m</sub>;

m is 3 or 4;

n is 1 or 2;

and pharmaceutically acceptable salts and solvates of the compounds of Formula I.

**Preferred compounds are:**

R<sup>1</sup> and R<sup>2</sup> are independently chosen from hydrogen, halogen, C<sub>1-6</sub>alkyl, trifluoromethyl, O-W, C<sub>1-6</sub>alkylthio, C<sub>1-6</sub>alkylsulfoxyl, C<sub>1-6</sub>alkylsulfonyl, or cyano;

- $R^3$  and  $R^4$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl, trifluoromethyl, or cyano;  
 $R^5$  can be hydrogen,  $C_{1-4}$ alkyl, halogen, trifluoromethyl, or  $C_{1-4}$ alkoxy;  
 $R^6$  and  $R^7$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl, or  $R^6$ ,  $R^7$  and the  
 5 carbon atom to which they are attached can form a cyclopropyl ring, or furthermore,  
 $R^7$  and  $R^8$  together can be  $(CH_2)_m$  to form a saturated heterocycle;  
 $R^8$  and  $R^9$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl;  
 $R^1$  to  $R^4$  cannot simultaneously be hydrogen;  
 $R^6$  and  $R^7$  cannot both be hydrogen;  
 10 W is hydrogen,  $C_{1-6}$ alkyl,  $C(=O)X$ , or  $P(=O)(OY)(OZ)$ ,  
 X is  $C_{1-6}$ alkyl,  $NR^8R^9$ ,  $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$ ,  $OC_{1-6}$ alkyl,  $C_{1-6}$ alkyl (which  
 can be substituted with halogen, hydroxyl,  $CO_2C_{1-4}$ alkyl,  $CON(C_{1-4}alkyl)_2$ ,  
 $C(=NH)NH_2$ ,  $NHC(=NH)NH_2$ ,  $NH_2$ ),  $C_{2-4}$ alkenyl (substituted by phenyl,  
 unsubstituted or substituted with one or more of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy or halogen);  
 15 Y and Z are independently chosen from hydrogen,  $C_{1-10}$ alkyl or Y and Z can together  
 form a lower alkyl chain of  $(CH_2)_m$ ;  
 m is 3;  
 n is 1 or 2;

20 **The more preferred compounds are:**

- where  $R^1$ ,  $R^3$ , and  $R^4$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl,  
 trifluoromethyl, or cyano;  
 $R^2$  is chosen from O-W;  
 $R^5$  can be hydrogen,  $C_{1-6}$ alkyl, halogen, trifluoromethyl, or  $C_{1-4}$ alkoxy;  
 25  $R^6$  is hydrogen and  $R^7$  is methyl;  
 $R^8$  and  $R^9$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl;  
 W is hydrogen,  $C_{1-4}$ alkyl, or  $C(=O)X$ ;  
 X is  $C_{1-6}$ alkyl,  $NR^8R^9$ , or  $N(R^8)CH_2(CH_2)_nC(=O)N(R^8)(R^9)$ ;  
 n is 1 or 2;

30 **The most preferred compounds are:**

- where  $R^1$ ,  $R^3$ , and  $R^4$  are independently chosen from hydrogen or halogen;  
 $R^2$  is O-W;  
 $R^5$  is hydrogen or  $C_{1-6}$ alkyl;  
 35  $R^6$  is hydrogen and  $R^7$  is methyl;  
 $R^8$  and  $R^9$  are hydrogen;  
 W is hydrogen,  $C_{1-4}$ alkyl;

It is recognized that compounds of Formula I can contain one or more chiral centers. This invention contemplates all enantiomers, diastereomers and, mixtures thereof.

5 In the above definitions, the total number of carbon atoms in a substituent group is indicated by the C<sub>i-j</sub> prefix where the numbers i and j define the number of carbon atoms; this definition includes straight chain, branched chain, and cyclic alkyl or (cyclic alkyl)alkyl groups.

10 It is important to recognize that a substituent may be present either singly or multiply when incorporated into the indicated structural unit. For example, the substituent halogen, which means fluorine, chlorine, bromine, or iodine, would indicate that the unit to which it is attached may be substituted with one or more halogen atoms, which may be the same or different.

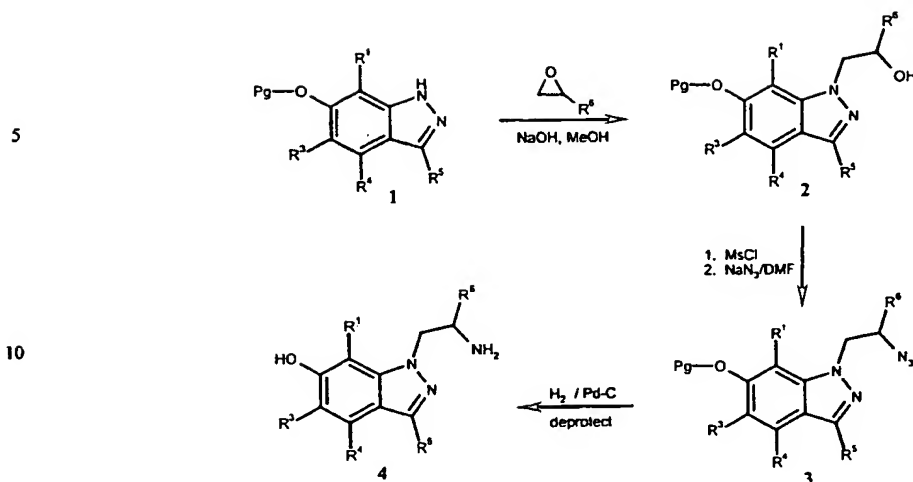
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### SYNTHESIS

The compounds of Formula I can be prepared by processes analogous to those known in the art. The preparation of compounds of Formula I wherein R<sup>2</sup> is OH and R<sup>1</sup> and R<sup>3</sup>-R<sup>5</sup> are as defined above can be prepared from the appropriate *O*-protected substituted-indazol-6-ol (1), suitable *O*-protective groups are e.g. methyl or benzyl, and can be prepared by methods well known in the art and described in Scheme 1 [U.S. Patent 5,494,928 (1997), WO98/30548 (1998)]. Alkylation of indazole 1 with the desired epoxide, e.g. propylene oxide, provides the intermediate alcohol 2.

20 Alternately, it can be advantageous for certain compounds to alkylate 1 using chloroacetone followed by reduction, e.g. with NaBH<sub>4</sub>, of the intermediate ketone to obtain the intermediate 2.

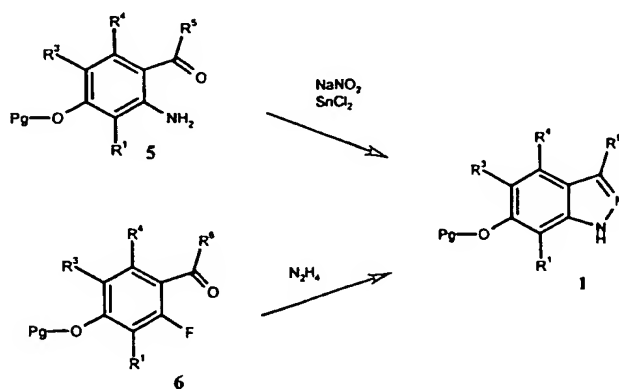
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SCHEME 1

The indazoles 1 can be prepared by conducting suitable functional group transformations on indazoles that are commercially available or that can be prepared according to literature procedures, generally starting from either the desired alkoxy-2-aminophenyl ketone (5), or the suitably substituted alkoxy-2-fluorophenyl ketone (6), depending on availability of suitable precursors (Scheme 2) [*J. Heterocycl. Chem.* 35, 895 (1998); *J. Med. Chem.* 40, 2706 (1997); *Comp. Heterocycl. Chem.* II, Vol. 3, 1 (1996)]. Also, certain indazoles 1 can be prepared from other indazoles 1 by direct substitution or by selective functional group transformations well known to the art.

SCHEME 2

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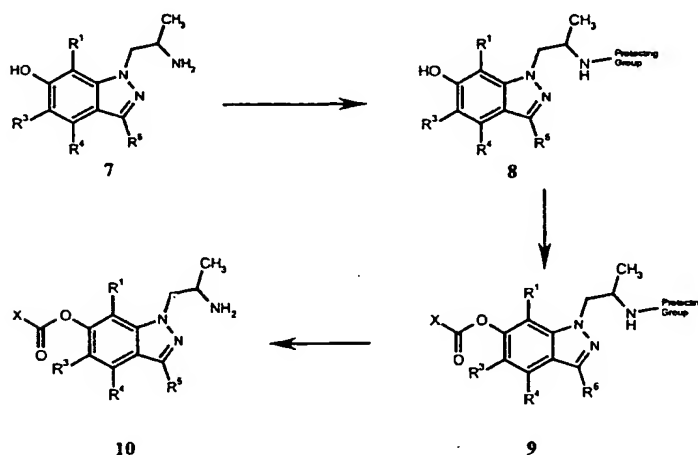
Intermediates 2 of Scheme 1 can also be prepared from the suitably substituted alkoxy-2-fluorophenyl ketones, for example by reaction of 6 with 1-hydrazino-2-



propanol [*J. Amer. Chem. Soc.* 76, 1283 (1954)] using procedures analogous to those known in the art [*J. Med. Chem.* 41, 5429 (1998)].

The compounds of Formula I wherein  $R^2$  is  $OC(=O)X$  can be prepared by procedures analogous to those known in the art. For example, when the substituent  $OC(=O)X$  is compatible with the subsequent reaction conditions as described above, such compounds can be prepared as described in Schemes 1 and 2. Alternately, and preferably, compounds of Formula I wherein  $R^2$  is  $OC(=O)X$  can be prepared by reacting the appropriate indazole 7, or preferably a suitable amino-protected intermediate, e.g. 8 (Scheme 3) with the desired activated acid derivative, such as an acid halide or active ester, or the like, to provide, for example, the esters 9. Removal of the N-protective group from the intermediate 9 provides the desired compounds 10 of Formula I.

### SCHEME 3



The indazole derivatives of interest for use as starting materials for the preparation of compounds 10 can be prepared by methods described above and in Scheme 1.

The compounds of this invention, Formula I, can be incorporated into various types of ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an implant). The compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity

enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 5 to 8. The compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.25% to 2% by weight. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled clinician.

The compounds can also be used in combination with other agents for treating glaucoma, such as, but not limited to,  $\beta$ -blockers (e.g., timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide),  $\alpha_1$  antagonists (e.g., nipradolol),  $\alpha_2$  agonists (e.g., iopidine and brimonidine), miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travaprost, unoprostone, and compounds set forth in U.S. Patent Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444, "hypotensive lipids" (e.g., lumigan and compounds set forth in 5,352,708), and neuroprotectants (e.g., compounds from U.S. Patent No. 4,690,931, particularly eliprodil and R-eliprodil, as set forth in a pending application U.S.S.N. 06/203350, and appropriate compounds from WO94/13275, including memantine.

The following examples are given to illustrate the preparation of compounds that are the subject of this invention but should not be construed as implying any

limitations to the claims. The preferred compounds of Formula I are described in Examples 2, 5 and 7. The most preferred is the compound of Example 2. The proton magnetic resonance spectrum of each compound of the Examples was consistent with the assigned structure

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### METHOD 1

#### **5-HT<sub>2</sub> Receptor Binding Assay**

In order to determine the relative affinities of serotonergic compounds at the 5-HT<sub>2</sub> receptors, their ability to compete for the binding of the agonist radioligand [<sup>125</sup>I]DOI to brain 5-HT<sub>2</sub> receptors is determined as described below with minor modification of the literature procedure [Neuropharmacology, 26, 1803 (1987)]. Aliquots of post mortem rat or human cerebral cortex homogenates (400 µl) dispersed in 50 mM TrisHCl buffer (pH 7.4) are incubated with [<sup>125</sup>I]DOI (80 pM final) in the absence or presence of methiothepin (10 µM final) to define total and non-specific binding, respectively, in a total volume of 0.5 ml. The assay mixture is incubated for 1 hour at 23°C in polypropylene tubes and the assays terminated by rapid vacuum filtration over Whatman GF/B glass fiber filters previously soaked in 0.3% polyethyleneimine using ice-cold buffer. Test compounds (at different concentrations) are substituted for methiothepin. Filter-bound radioactivity is determined by scintillation spectrometry on a beta counter. The data are analyzed using a non-linear, iterative curve-fitting computer program [Trends Pharmacol. Sci., 16, 413 (1995)] to determine the compound affinity parameter. The concentration of the compound needed to inhibit the [<sup>125</sup>I]DOI binding by 50% of the maximum is termed the IC<sub>50</sub> value. A compound is considered to possess high affinity for the 5-HT<sub>2</sub> receptor if the IC<sub>50</sub> value is less than 50 nM.

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### METHOD 2

#### **5-HT<sub>2</sub> Functional Assay: Phosphoinositide (PI) turnover assay**

30

The relative agonist activity of serotonergic compounds at the 5-HT<sub>2</sub> receptor can be determined in vitro using the ability of the compounds to stimulate the production of [<sup>3</sup>H]inositol phosphates in [<sup>3</sup>H]myo-inositol-labeled A7r5 rat vascular smooth muscle cells by their ability to activate the enzyme phospholipase C. These cells are grown in culture plates, maintained in a humidified atmosphere of 5% CO<sub>2</sub> and 95% air and fed semi-weekly with Dulbecco's modified Eagle medium (DMEM) containing 4.5 g/l glucose and supplemented with 2mM glutamine, 10 µg/ml gentamicin, and 10% fetal bovine serum. For the purpose of conducting the

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phosphoinositide (PI) turnover experiments, the A7r5 cells are cultured in 24-well plates as previously [J. Pharmacol. Expt. Ther., 286, 411 (1998)]. Confluent cells are exposed for 24-30 hrs to 1.5  $\mu$ Ci [ $^3$ H]-myo-inositol (18.3 Ci/mmol) in 0.5 ml of serum-free medium. Cells are then rinsed once with DMEM/F-12 containing 10 mM LiCl prior to incubation with the test agent (or solvent as the control) in 1.0 ml of the same medium for 1 hr at 37°C, after which the medium is aspirated and 1 ml of cold 0.1 M formic acid added to stop the reaction. The chromatographic separation of [ $^3$ H]-inositol phosphates ([ $^3$ H]-IPs) on an AG-1-X8 column is performed as previously described [J. Pharmacol. Expt. Ther. 286, 411 (1998)] with sequential washes with H<sub>2</sub>O and 50 mM ammonium formate, followed by elution of the total [ $^3$ H]-IPs fraction with 1.2 M ammonium formate containing 0.1 M formic acid. The eluate (4 ml) is collected, mixed with 15 ml scintillation fluid, and the total [ $^3$ H]-IPs determined by scintillation counting on a beta-counter. Concentration-response data are analyzed by the sigmoidal fit function of the Origin Scientific Graphics software (Microcal Software, Northampton, MA) to determine agonist potency (EC<sub>50</sub> value) and efficacy (E<sub>max</sub>). Serotonin (5-HT) is used as a positive control (standard) agonist compound and the efficacy of test compounds is compared to that of 5-HT (set at 100%). The concentration of the compound needed to stimulate the production of [ $^3$ H]-IPs by 50% of the maximum response is termed the EC<sub>50</sub> value. Compounds are considered potent agonists if their EC<sub>50</sub> values in this functional assay are  $\leq 1$   $\mu$ M and are considered full agonists if their efficacy is  $> 80\%$  of that of 5-HT.

The above procedures were used to generate the data shown in Table 1.

**Table 1. 5-HT<sub>2</sub> Receptor Binding and Functional Data.**

Compound	IC <sub>50</sub> , nM	EC <sub>50</sub> , nM	Efficacy (E <sub>max</sub> , %)
$\alpha$ -Methylserotonin	3.5	189	104
Example 1	3.1	578	71
Example 2	3.0	483	87
Example 4	-	243	73
Example 5	2.0	541	64
Example 6	2.2	1050	84

**EXAMPLE 1****2-(6-Methoxy-3-methyl-indazol-1-yl)-1-methylethylamine fumarate****Step A: 6-Methoxy-3-methyl-1H-indazole**

5 To a solution of 2-fluoro-4-methoxyacetophenone (1.90 g, 11.3 mmol) in ethanol (20 ml) was added hydrazine hydrate (1.4 ml, 45.0 mmol) and heated at reflux temperature for 6 h. This mixture was evaporated to a residue and ethylene glycol (10 ml) was added. The mixture was heated at 150 °C for 18 h, cooled to room temperature, diluted with water (50 ml), and extracted with dichloromethane (3 x 60  
10 ml). The combined extracts were washed with brine (10 ml), dried (MgSO<sub>4</sub>) and evaporated to a residue, which was crystallized from ethyl acetate to give a solid (1.1 g, 59%): MS(ES) *m/z* 163 (M<sup>+</sup>).

**Step B: 1-(6-Methoxy-3-methyl-indazol-1-yl)-propan-2-one**

15 To a solution of the product from Step A (1.1 g, 6.7 mmol) in DMF (10 ml) was added sodium hydride (60% in oil, 0.41 g, 10.2 mmol) at room temperature. After stirring for 30 min, chloroacetone (0.79 ml, 10.2 mmol) was added, and the solution heated at 60 °C for 6 h. The reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (10 ml) and extracted with ethyl acetate (3 x  
20 65 ml). The combined extracts were washed with brine (10ml), dried (MgSO<sub>4</sub>), and evaporated to give a residue which was purified by chromatography (silica, 20% to 30% ethyl acetate in hexane) to give an oil (1.3 g, 88%): MS (ES) *m/z* 219 (M<sup>+</sup>).

**Step C: 1-(6-Methoxy-3-methyl-indazol-1-yl)-propan-2-ol**

25 Sodium borohydride (0.21 g, 5.5 mmol) was added to a solution of the product from Step B (1.2 g, 5.5 mmol) in MeOH (10 ml) at room temperature. After stirring for 2 h at room temperature the solvent was evaporated and a saturated aqueous solution of ammonium chloride (10 mL) was added to the residue; this mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with  
30 brine (10 ml), dried (MgSO<sub>4</sub>) and evaporated to a residue which was purified by chromatography (silica, 20% to 30% ethyl acetate in hexane) to give an oil (0.68 g, 56%): MS (ES) *m/z* 221 (M<sup>+</sup>).

**Step D: 1-(2-Azido-propyl)-6-methoxy-3-methyl-1H-indazole**

35 To a solution of the product from Step C (0.66 g, 3.0 mmol) in dichloromethane (10 ml) at 0 °C was added triethylamine (0.55 ml, 3.9 mmol) and methanesulfonyl chloride (0.31 ml, 3.9 mmol). After stirring for 30 min, ether (50 ml) and water (50 ml) were added. The organic layer was separated and the aqueous

extracted with ether (2 x 50 ml). The combined ether extracts were washed with brine (30 ml), dried (MgSO<sub>4</sub>), and evaporated. The residue was taken up in DMF (6 ml) and sodium azide (0.26 g, 3.9 mmol) added. This mixture was heated at 70 °C for 12 h, poured into water, and extracted with ether (3 x 50 ml). The combined extracts  
5 were washed with brine, dried (MgSO<sub>4</sub>), and evaporated to a residue, which was purified by chromatography (silica, hexane to 10% ethyl acetate in hexane) to give an oil (0.51 g, 69%): MS (ES) *m/z* 246 (M<sup>+</sup>).

**Step E: 2-(6-Methoxy-3-methyl-indazol-1-yl)-1-methylethylamine fumarate**

10 To a solution of the product from Step D (0.50 g, 2.0 mmol) in methanol at room temperature was added palladium-on-carbon (10%, 0.10 g). This suspension was stirred for 18 h under an atmosphere of hydrogen. The reaction mixture was filtered through a filter aid and the filtrate evaporated to a residue (0.43 g, 96%) which was converted to the fumaric acid salt and crystallized from methanol/ether to give a  
15 colorless solid (0.27 g): mp 150-152 °C; MS (ES) *m/z* 191 (M<sup>+</sup>). Analysis. Calculated for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O · 1.0 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub> · 1.0 CH<sub>3</sub>OH: C, 55.58; H, 6.86; N, 11.44. Found: C, 55.41; H, 6.85; N, 11.37.

**EXAMPLE 2**

**1-(2-Aminopropyl)-3-methyl-1*H*-indazol-6-ol fumarate**

**Step A: 1-(4-Benzyloxy-2-fluoro-phenyl)-ethanone**

Potassium carbonate (5.5 g, 40.0 mmol) and benzyl bromide (4.6 ml, 38.9 mmol) were added to a solution of 2-fluoro-4-hydroxyacetophenone (5.0 g, 32.4  
25 mmol) in ethanol (50 ml), and the mixture was heated at reflux temperature for 16 h. The reaction mixture was evaporated to a residue to which 2 N HCl (100 ml) was added. This mixture was extracted with ethyl ether (3 x 60 ml) and the combined extracts were washed with brine (10 ml), dried (MgSO<sub>4</sub>), and evaporated to a residue, which was crystallized from ethyl acetate (7.4 g, 93%): MS(ES) *m/z* 245 (M<sup>+</sup>).

**Step B: 6-Benzyloxy-3-methyl-1*H*-indazole**

A solution of the product from Step A (7.4 g, 30.3 mmol) in ethanol (20 mL) was treated as described for Example 1, Step A to give a colorless solid (6.1 g, 69%): MS(ES) *m/z* 239 (M<sup>+</sup>).

**Step C: 1-(6-Benzyloxy-3-methyl-indazol-1-yl)-propan-2-one**

A solution of the product from Step B (2.3 g, 9.7 mmol) in DMF (10 ml) was treated by the sequence described for Example 1, Step B to give a residue, which was used in the next step without further purification: MS (ES)  $m/z$  295 ( $M^+$ ).

**Step D: 1-(6-Benzyloxy-3-methyl-indazol-1-yl)-propan-2-ol**

A solution of the product from Step C (3.3 g, 5.5 mmol) in MeOH (10 ml) was treated as described for Example 1, Step C to give an oil (0.30 g, 10%): MS (ES)  $m/z$  297 ( $M^+$ ).

**Step E: 1-(2-Azido-propyl)-6-benzyloxy-3-methyl-1H-indazole**

A solution of the product from Step D (0.28 g, 0.95 mmol) in dichloromethane (10 ml) was treated by the sequence described for Example 1, Step D to give an oil (0.16 g, 52%): MS (ES)  $m/z$  322 ( $M^+$ ).

**Step F: 1-(2-Aminopropyl)-3-methyl-1H-indazol-6-ol fumarate**

A solution of the product from Step E (0.16 g, 0.50 mmol) in methanol was treated as described for Example 1, Step E to give a residue (0.10 g, 97%) which was converted to fumaric acid salt and crystallized from a mixture of methanol and ether to give a colorless solid (0.11 g): mp:166-168 °C; MS(ES)  $m/z$  206 ( $M^+$ ). Analysis. Calculated for  $C_{11}H_{15}N_3O \cdot 1.8 C_4H_4O_4$ : C, 52.78; H, 5.40; N, 10.15. Found: C, 52.45; H, 5.53; N, 10.29.

**EXAMPLE 3****2,2-Dimethyl-propionic acid 1-(2-aminopropyl)-1H-indazol-6-yl ester fumarate****Step A: 2,2-Dimethyl-propionic acid 1H-indazol-6-yl ester**

To a solution of 1H-indazol-6-ol (0.88 g, 6.6 mmol) in dichloromethane (10 ml) at room temperature was added triethylamine (0.98 ml, 7.0 mmol) and DMAP (0.05 g) followed by trimethylacetyl chloride (0.82 ml, 6.6 mmol). After stirring for 1 h, the mixture was diluted with saturated aqueous solution of ammonium chloride (20 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with brine (10 ml), dried ( $MgSO_4$ ), and evaporated to a residue which was purified by chromatography (silica, 10% to 20% ethyl acetate in hexane) to give an oil (1.1 g, 76%):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.15 (d,  $J = 0.8$  Hz, 1H), 8.01 (s, 1H), 7.75 (s, 1H), 7.58 (d,  $J = 8.6$  Hz, 1H), 7.01 and 6.96 (dd,  $J = 2.0$  and 8.6 Hz, 1H), 1.59 (s, 9H); MS(ES)  $m/z$  219 ( $M^+$ ).

**Step B: 2,2-Dimethyl-propionic acid 1-(2-oxo-propyl)-1*H*-indazol-6-yl ester**

A solution of the product of Step A (1.5g, 6.9 mmol) in DMF (10 ml) was treated by the procedure described for Example 1, Step B to give an oil (1.3 g, 62%): <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.09 (d, J = 0.8 Hz, 1H), 7.99 (s, 1H), 7.90 (s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.01 and 6.96 (dd, J = 2.0 and 8.6 Hz, 1H), 4.64 (s, 2H), 2.15 (s, 3H), 1.56 (s, 3H) 1.27 (s, 6H); MS(ES) *m/z* 275 (M<sup>+</sup>).

**Step C: 2,2-Dimethyl-propionic acid 1-(2-hydroxy-propyl)-1*H*-indazol-6-yl ester**

A solution of the product of Step B (0.91g, 3.6 mmol) in methanol (10 ml) was treated by the procedure described for Example 1, Step C to give an oil (0.79 g, 86%) that was used in the next reaction with further purification: <sup>1</sup>H NMR δ (CDCl<sub>3</sub>) 7.99 (s, 1H), 7.98 (s, 1H), 7.60 (d, J = 8.6 Hz, 1H), 7.01 and 6.96 (dd, J = 2.0 and 8.6 Hz, 1H), 4.14-3.89 (m, 3H), 1.56 (s, 3H) 1.32 (s, 9H).

**Step D: 2,2-Dimethyl-propionic acid 1-(2-azido-propyl)-1*H*-indazol-6-yl ester**

A solution of the product from Step C (1.70 g, 6.2 mmol) in dichloromethane (10 ml) was treated by the procedure described for Example 1, Step D to give an oil (1.30 g, 69%): MS(ES) *m/z* 274 (M<sup>+</sup>-28).

**Step E: 2,2-Dimethyl-propionic acid 1-(2-aminopropyl)-1*H*-indazol-6-yl ester fumarate**

A solution of the Product from Step D (1.25 g, 4.1 mmol) in methanol was treated by the procedure described for Example 1, Step E to give an oil (0.13 g, 88%) which was treated with fumaric acid; the salt which formed was crystallized from a mixture of methanol and ether to give a colorless solid: mp 180-182 °C; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 8.37 (s, 1H), 7.89 (s, 1H), 7.82 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 6.45 (s, 2H), 4.18-4.01 (m, 2H), 3.5 (m, 1H), 1.50 (s, 9H) 1.30 (d, J = 6.6 Hz, 3H); MS(ES) *m/z* 276 (M<sup>+</sup>). Analysis. Calculated for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> · 1.2 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>: C, 57.36; H, 6.27; N, 10.13. Found: C, 56.98; H, 6.57; N, 10.22.

**EXAMPLE 4****2-(6-Methoxy-indazol-1-yl)-1-methyl-ethylamine****Step A: [2-(6-Hydroxy-indazol-1-yl)-1-methyl-ethyl]-carbamic acid benzyl ester**

To a solution of 1-(2-aminopropyl)-indazol-6-ol (0.46 g, 2.4 mmol) in THF (10.0 mL) was added a saturated aqueous solution of sodium bicarbonate (2.0 mL) followed by benzyl chloroformate (0.40 mL) at room temperature. After stirring for 1 h, the solution was diluted with 1 N HCl (10 mL) and ammonium chloride (20 mL)



followed by extraction with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine (10 mL), dried (MgSO<sub>4</sub>) and evaporated to give a residue which was used in the next step without further purification (0.75 g, 98%); MS (ES) *m/z* 326 (M<sup>+</sup>).

5

**Step B: [2-(6-Methoxy-indazol-1-yl)-1-methyl-ethyl]-carbamic acid benzyl ester**

To a solution of the product from Step A (0.95 g, 3.19 mmol) in DMF (10 mL) was added cesium carbonate (1.26 g, 3.70 mmol) followed by iodomethane (0.23 mL, 3.70 mmol) at room temperature. After stirring for 3 h, saturated aqueous ammonium chloride (30 mL) was added and the mixture extracted with ethyl acetate (3 x 65 mL). The combined extracts were washed with brine (10 mL), dried (MgSO<sub>4</sub>) and evaporated to a residue which was purified by chromatography (silica, 20% ethyl acetate in hexane to 30% ethyl acetate in hexane) to give a syrup (0.63 g, 92%); MS (ES) *m/z* 340(M<sup>+</sup>).

15

**Step C: 2-(6-Methoxy-indazol-1-yl)-1-methyl-ethylamine**

To a solution of the product from Step B (0.68 g, 2.0 mmol) in methanol was added Pd/C (10%, 0.10 g) under a nitrogen atmosphere at room temperature. The mixture was stirred for 20 h under a hydrogen atmosphere and filtered through a filter aid. The filtrate was evaporated to a residue which was purified by chromatography (silica, 5% methanol in dichloromethane to 10% methanol in dichloromethane) to give a syrup (0.40 g, 97%). Treatment of the syrup with fumaric acid gave a residue that was recrystallized from methanol/ether to provide a colorless solid: mp 151-152°C; MS (ES) *m/z* 206 (M<sup>+</sup>). Analysis. Calculated for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O · 1.0 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub> · 1.0 H<sub>2</sub>O: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.88; H, 6.31; N, 12.14.

25

**EXAMPLE 5**

**2-(3-Chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine**

**Step A: 2-Hydrazino-4-methoxy-benzoic acid**

A suspension of 2-acetylamino-4-methoxy-benzoic acid (15 g, 73.7 mmol) in water (75 mL) was cooled to -5°C and conc HCl (150 mL) was added followed by cooling to -5°. To this mixture was added a solution of NaNO<sub>2</sub> (5.43 g, 77.4 mmol) in water (50 mL) that had been cooled to -5°; this solution was added at such a rate so as to maintain the temperature of the reaction mixture between -5° and 0°C. The reaction mixture was stirred for 10 min and the clear solution was added to a solution of stannous chloride (41.9 g, 221 mmol) in conc HCl (150 mL) that had been cooled to -20°C. This addition was conducted so as to maintain a temperature of -20° to -

35

10°C for the reaction mixture, followed by stirring the mixture for 1.5 h at -20°C. The solid that formed was collected by filtration, washed with chilled EtOH, and dried to give an off-white solid (10.8 g): APCI/LCMS m/z 183 (M+H)<sup>+</sup>.

5     **Step B: 6-Methoxy-1*H*-indazol-3-ol**

A mixture of the product from Step A (10.5 g, 48 mmol), water (250 mL), and conc HCl (2.5 mL) was refluxed for 30 min. The volume of the reaction mixture was reduced by evaporation (ca 100 mL) and the pH adjusted to 7 by the slow addition of a saturated aqueous solution of sodium carbonate at room temperature. The solid that  
10     formed upon standing was collected and dried to give a gray solid (6.8 g): APCI/LCMS m/z 165 (M+H)<sup>+</sup>.

**Step C: 3-Chloro-6-methoxy-1*H*-indazole**

To a solution of the product from Step B (1 g, 6.1 mmol) in pyridine (0.5 mL,  
15     6.1 mmol) was added phosphorous oxychloride (0.9 mL, 9.2 mmol) and the mixture heated at 130-140°C for 5 h. The reaction mixture was cooled to 70°C and poured onto ice (100 g). After standing for 24 h, the solid was collected and dried to give a cream-colored solid (0.42 g): ES/LCMS m/z 181 (M-H)<sup>+</sup>.

20     **Step D: [2-(3-Chloro-6-methoxy-indazol-1-yl)-1-methyl-ethyl]-carbamic acid benzyl ester**

To a solution of the product from Step C (0.18 g, 1 mmol) and (2-bromo-1-methyl-ethyl)-carbamic acid benzyl ester (0.27 g, 1 mmol) in DMF (2 mL) was added potassium carbonate (0.17 g, 1.2 mmol) and the mixture stirred at 75° for 18 h. Ethyl  
25     acetate (20 mL) and water (20 mL) were added to the reaction mixture and the aqueous layer was separated and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (30 mL), dried (MgSO<sub>4</sub>), and evaporated to a residue that was purified by chromatography (silica, hexane to 15% ethyl acetate in hexane) to give a syrup (0.27 g): APCI/LCMS m/z 374 (M+H)<sup>+</sup>.

30

**Step E: 2-(3-Chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine**

To a solution of the product from Step D (0.15 g, 0.4 mmol) in 1,2-dichloroethane (4 mL) under nitrogen was added boron tribromide-dimethylsulfide complex (2.4 mmol, 2.4 mL of a 1 N solution in 1,2-dichloroethane) and the mixture  
35     was heated at 84°C for 3 h. After cooling, saturated aqueous sodium bicarbonate (5 mL) was added and the mixture was extracted with chloroform (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried (MgSO<sub>4</sub>), and purified by chromatography (C-18 RP-HPLC, 5% acetonitrile/water to 70% acetonitrile/water

containing 0.1% trifluoroacetic acid) to give a residue (0.03 g) that was converted to the dihydrochloride salt: ESI/LCMS  $m/z$  240 (M+H)<sup>+</sup>.

#### **EXAMPLE 6**

5

#### **1-(2-Aminopropyl)-3-chloro-1*H*-indazol-6-ol**

A solution of the product from Example 5, Step D (0.1 g, 0.27 mmol) was treated as described in Step E of Example 5 but the reaction mixture was heated for 8 h to give a syrup (0.015 g), which was converted to the dihydrochloride salt:

10

ESI/LCMS  $m/z$  226 (M+H)<sup>+</sup>.

#### **EXAMPLE 7**

<b>Ingredients</b>	<b>Amount (wt %)</b>
1-(2-Aminopropyl)-3-methyl-1 <i>H</i> -indazol-6-ol fumarate	0.01 – 2%
Hydroxypropyl methylcellulose	0.5%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.4
Purified water	q.s. to 100%

**EXAMPLE 8**

Ingredients	Amount (wt %)
1-(2-Aminopropyl)-3-methyl-1 <i>H</i> -indazol-6-ol fumarate	0.01 – 2%
Methyl cellulose	4.0%
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH to 7.4
Purified water	q.s. to 100%

**EXAMPLE 9**

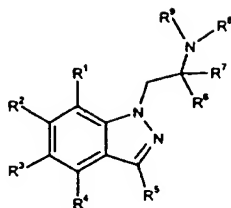
Ingredients	Amount (wt %)
1-(2-Aminopropyl)-3-methyl-1 <i>H</i> -indazol-6-ol fumarate	0.01 – 2%
Guar gum	0.4- 6.0%
Dibasic sodium phosphate (anhydrous)	0.2%-
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH
Purified water	q.s. to 100%

**EXAMPLE 10**

<b>Ingredients</b>	<b>Amount (wt %)</b>
1-(2-Aminopropyl)-3-methyl-1 <i>H</i> -indazol-6-ol fumarate	0.01 – 2%
White petrolatum and mineral oil and lanolin	Ointment consistency
Dibasic sodium phosphate (anhydrous)	0.2%
Sodium chloride	0.5%
Disodium EDTA (Edetate disodium)	0.01%
Polysorbate 80	0.05%
Benzalkonium chloride	0.01%
Sodium hydroxide / Hydrochloric acid	For adjusting pH

**We Claim:**

1. A compound of the formula:



5 wherein  $R^1$  to  $R^4$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl, trifluoromethyl, O-W,  $C_{1-6}$ alkylthio,  $C_{1-6}$ alkylsulfoxyl,  $C_{1-6}$ alkylsulfonyl, or cyano;  $R^5$  can be halogen, trifluoromethyl, cyano,  $NR^{10}R^{11}$ ;  $R^6$  and  $R^7$  are independently chosen from hydrogen,  $C_{1-4}$ alkyl or  $R^6$ ,  $R^7$  and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore,  $R^7$  and  $R^8$  together can be  $(CH_2)_m$  to form a saturated heterocycle;  $R^8$  and  $R^9$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl;  $R^{10}$  and  $R^{11}$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl, or  $R^{10}$ ,  $R^{11}$  and the nitrogen atom to which they are attached can form a saturated heterocyclic ring  
10 selected from pyrrolidine, piperidine, piperazine, or morpholine;  $R^1$  to  $R^4$  cannot simultaneously be hydrogen;  $R^6$  and  $R^7$  cannot both be hydrogen; W is hydrogen,  $C_{1-4}$ alkyl,  $C(=O)X$ , or  $P(=O)(OY)(OZ)$ ; X is  $C_{1-6}$ alkyl,  $NR^8R^9$ ,  $N(R^8)CH_2(CH_2)_nC(=O)N(R^8)(R^9)$ ,  $OC_{1-6}$ alkyl,  $C_{1-6}$ alkyl (which can be substituted with halogen, hydroxyl,  $CO_2C_{1-4}$ alkyl,  $CON(C_{1-4}$ alkyl)<sub>2</sub>,  $C(=NH)NH_2$ ,  $NHC(=NH)NH_2$ ,  $NH_2$ ),  $C_{2-4}$ alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy or halogen); Y and Z are independently chosen from hydrogen,  $C_{1-10}$  alkyl or Y and Z can together form a lower alkyl chain of  $(CH_2)_m$ ;  
15 m is 3 or 4; n is 1 or 2; and pharmaceutically acceptable salts and solvates of the compounds.

2. The compound of Claim 1 wherein:

$R^1$  and  $R^2$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl, trifluoromethyl, O-W,  $C_{1-6}$ alkylthio,  $C_{1-6}$ alkylsulfoxyl,  $C_{1-6}$ alkylsulfonyl, or cyano;

5  $R^3$  and  $R^4$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl, trifluoromethyl, or cyano;

$R^5$  can be hydrogen,  $C_{1-4}$ alkyl, halogen, trifluoromethyl, or  $C_{1-4}$ alkoxy;

$R^6$  and  $R^7$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl, or  $R^6$ ,  $R^7$  and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore,

10  $R^7$  and  $R^8$  together can be  $(CH_2)_m$  to form a saturated heterocycle;

$R^8$  and  $R^9$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl;

$R^1$  to  $R^4$  cannot simultaneously be hydrogen;

$R^6$  and  $R^7$  cannot both be hydrogen;

W is hydrogen,  $C_{1-6}$ alkyl,  $C(=O)X$ , or  $P(=O)(OY)(OZ)$ ,

15 X is  $C_{1-6}$ alkyl,  $NR^8R^9$ ,  $N(R^8)CH_2(CH_2)_nC(=O)NR^8R^9$ ,  $OC_{1-6}$ alkyl,  $C_{1-6}$ alkyl (which can be substituted with halogen, hydroxyl,  $CO_2C_{1-4}$ alkyl,  $CON(C_{1-4}alkyl)_2$ ,

$C(=NH)NH_2$ ,  $NHC(=NH)NH_2$ ,  $NH_2$ ),  $C_{2-4}$ alkenyl (substituted by phenyl,

unsubstituted or substituted with one or more of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy or halogen);

Y and Z are independently chosen from hydrogen,  $C_{1-10}$ alkyl or Y and Z can together

20 form a lower alkyl chain of  $(CH_2)_m$ ;

m is 3;

n is 1 or 2;

3. The compound of Claim 1 wherein:

25  $R^1$ ,  $R^3$ , and  $R^4$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl, trifluoromethyl, or cyano;

$R^2$  is chosen from O-W;

$R^5$  can be hydrogen,  $C_{1-6}$ alkyl, halogen, trifluoromethyl, or  $C_{1-4}$ alkoxy;

$R^6$  is hydrogen and  $R^7$  is methyl;

30  $R^8$  and  $R^9$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl;

W is hydrogen,  $C_{1-4}$ alkyl, or  $C(=O)X$ ;

X is  $C_{1-6}$ alkyl,  $NR^8R^9$ , or  $N(R^8)CH_2(CH_2)_nC(=O)N(R^8)(R^9)$ ;

n is 1 or 2;

35 4. The compound of Claim 1 wherein:

$R^1$ ,  $R^3$ , and  $R^4$  are independently chosen from hydrogen or halogen;

$R^2$  is O-W;

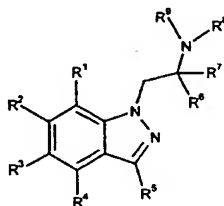
$R^5$  is hydrogen or  $C_{1-6}$ alkyl;

$R^6$  is hydrogen and  $R^7$  is methyl;

$R^8$  and  $R^9$  are hydrogen;

W is hydrogen,  $C_{1-4}$ alkyl;

- 5        5.        The compound of Claim 1 selected from the group consisting of:  
           1-(2-aminopropyl)-3-methyl-1*H*-indazol-6-ol fumarate  
           2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine  
           1-(2-aminopropyl)-3-methyl-1*H*-indazol-6-ol fumarate
- 10       6.        A topical ophthalmic composition for lowering and controlling normal or  
           elevated IOP and treating glaucoma, comprising a pharmaceutically effective amount  
           of a compound of Claim 1, 2, 3, 4, or 5.
- 15       7.        A method for lowering and controlling normal or elevated IOP and treating  
           glaucoma, which comprises administering a pharmaceutically effective amount of a  
           compound of Claim 1, 2, 3, 4, or 5.
- 20       8.        A method for lowering and controlling normal or elevated IOP and treating  
           glaucoma, which comprises administering a pharmaceutically effective amount of a  
           compound of the formula:



- wherein  $R^1$  to  $R^4$  are independently chosen from hydrogen, halogen,  $C_{1-6}$ alkyl, trifluoromethyl, O-W,  $C_{1-6}$ alkylthio,  $C_{1-6}$ alkylsulfoxyl,  $C_{1-6}$ alkylsulfonyl, or cyano;
- 25        $R^5$  can be hydrogen,  $C_{1-6}$ alkyl, or  $C_{1-4}$ alkoxy, halogen, trifluoromethyl, cyano,  $NR^{10}R^{11}$ ;
- $R^6$  and  $R^7$  are independently chosen from hydrogen,  $C_{1-4}$ alkyl or  $R^6$ ,  $R^7$  and the carbon atom to which they are attached can form a cyclopropyl ring, or furthermore,  $R^7$  and
- 30        $R^8$  together can be  $(CH_2)_m$  to form a saturated heterocycle;
- $R^8$  and  $R^9$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl;



$R^{10}$  and  $R^{11}$  are independently chosen from hydrogen or  $C_{1-4}$ alkyl, or  $R^{10}$ ,  $R^{11}$  and the nitrogen atom to which they are attached can form a saturated heterocyclic ring selected from pyrrolidine, piperidine, piperazine, or morpholine;

$R^1$  to  $R^4$  cannot simultaneously be hydrogen;

5  $R^6$  and  $R^7$  cannot both be hydrogen;

W is hydrogen,  $C_{1-4}$ alkyl,  $C(=O)X$ , or  $P(=O)(OY)(OZ)$ ;

X is  $C_{1-6}$ alkyl,  $NR^8R^9$ ,  $N(R^8)CH_2(CH_2)_nC(=O)N(R^8)(R^9)$ ,  $OC_{1-6}$ alkyl,  $C_{1-6}$ alkyl (which can be substituted with halogen, hydroxyl,  $CO_2C_{1-4}$ alkyl,  $CON(C_{1-4}alkyl)_2$ ,

10  $C(=NH)NH_2$ ,  $NHC(=NH)NH_2$ ,  $NH_2$ ),  $C_{2-4}$ alkenyl (substituted by phenyl, unsubstituted or substituted with one or more of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy or halogen);

Y and Z are independently chosen from hydrogen,  $C_{1-10}$  alkyl or Y and Z can together form a lower alkyl chain of  $(CH_2)_m$ ;

m is 2 – 4;

n is 1 or 2;

15 and pharmaceutically acceptable salts and solvates of the compounds.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/31247

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D231/56 A61K31/416 A61P27/06

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 12481 A (BENTLEY JONATHAN MARK ;GEORGE ASHLEY ROGER (GB); HAMLYN RICHARD JO) 9 March 2000 (2000-03-09) cited in the application page 15 -page 17, line 3; claims; examples	1-8
P,Y	WO 00 17170 A (BENTLEY JONATHAN MARK ;ADAMS DAVID REGINALD (GB); CEREBRUS PHARM L) 30 March 2000 (2000-03-30) cited in the application page 15, line 9 -page 17, line 19; claims; examples	1-8
P,Y	WO 00 16761 A (ALCON LAB INC ;DEAN THOMAS R (US); MAY JESSE A (US); SHARIF NAJAM) 30 March 2000 (2000-03-30) cited in the application claim 1	1-8
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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Date of the actual completion of the international search

26 January 2001

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 59499 A (ALCON LAB INC ;DEAN THOMAS R (US); MAY JESSE A (US); SHARIF NAJAM) 25 November 1999 (1999-11-25) page 1, line 14 -page 4, line 10 ----	1-8
A	SUGRUE M F: "NEW APPROACHES TO ANTIGLAUCOMA THERAPY" JOURNAL OF MEDICINAL CHEMISTRY,US,AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 40, no. 18, 29 August 1997 (1997-08-29), pages 2793-2809, XP000878913 ISSN: 0022-2623 the whole document -----	1-8
A	EP 0 985 414 A (PFIZER PROD INC) 15 March 2000 (2000-03-15) claim 1; table 1 -----	1-8

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In Application No  
PCT/US 00/31247

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WO 0016761	A	30-03-2000	AU 6132699 A	10-04-2000
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			JP 2000026297 A	25-01-2000